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Factor associated with and risk of cardiovascular disease in people with uncontrolled hypertension

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We aimed to identify and validate factors related to uncontrolled hypertension. Participants treated with at least one antihypertensive drug from the prospective contemporaneous CoLaus|PsyCoLaus study were enrolled. We investigated the association between hypertension status (uncontrolled, defined as systolic blood pressure [SBP] ≥ 140 mm Hg and/or diastolic blood pressure [DBP] ≥ 90 mm Hg, versus controlled hypertension [SBP/DBP < 140/90 mm Hg]) and potential risk factors. Additionally, the prospective association of uncontrolled hypertension with cardiovascular disease and all-cause mortality was evaluated. 1040 participants recruited between 2003 and 2006 with a mean follow-up of 12.3 years (SD ± 3.4) were included in the analyses. Heavy alcohol consumption, increased BMI, increased ferritin and albuminuria were positively associated with uncontrolled hypertension. Factors inversely associated with uncontrolled hypertension were university degree, current smoker, and high potassium urinary excretion. Uncontrolled hypertension status was not associated with incident ASCVD nor all-cause mortality in our study. In conclusion, uncontrolled hypertension was associated with modifiable factors, such as heavy drinking, obesity and level of education. Further studies should investigate whether including biological markers in clinical practice, such as potassium excretion, ferritin levels, or albuminuria, would help identify individuals who may develop uncontrolled hypertension.

Keywords Uncontrolled hypertension, Characteristics, Cardiovascular risk, Prospective study

Hypertension is the leading preventable risk factor for cardiovascular disease. It affects approximately 1.13 billion people worldwide, with over 150 million only in Europe and approximately 1.5 million in Switzerland[1–3].

According to the 2021 ESC/EHC guidelines, blood pressure (BP) targets for any individual are < 140/90 mm Hg, while ideal targets are < 130/80 mm Hg in people < 70 years and < 140/80 mm Hg in older people who do not tolerate lower values[4]. Lifestyle changes, such as healthy dietary habits and physical activity, associated with antihypertensive drugs are recommended to achieve these goals[1]. Unfortunately, over half of the treated people present uncontrolled hypertension (i.e., not reaching target BP < 140/90 mm Hg) with significant health consequences such as cardiovascular disease, chronic kidney disease and a higher cardiovascular and all-cause mortality[2,5–9].

Studies indicate that identifying poor adherence to treatment and enhancing physician clinical actions when BP is uncontrolled have a significant impact on BP control[1].Currently, according to previous literature, factors such as old age, obesity, excess sodium intake, low potassium intake, albuminuria, higher creatinine levels, and/or diabetes mellitus have been associated with uncontrolled or resistant hypertension[1,4,6–13]. However, these factors are not yet incorporated into current primary care guidelines for target potential uncontrolled BP.

Using prospective data from the CoLaus|PsycoLaus study of middle-aged adults, the main aim of our study was to identify or validate, with contemporaneous material, conditions associated with uncontrolled hypertension. The aim of this approach is to refine the targeting of individuals at risk for physician, to enable more personalized treatment adjustments. The second aim was to determine whether uncontrolled hypertension was associated with the development of atherosclerotic cardiovascular disease (ASCVD) and all-cause mortality.

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Results

Study participants

From the 6733 participants initially enrolled in the CoLaus|PsyCoLaus study at baseline, 1202 reported taking at least one antihypertensive drug. After excluding 162 participants based on selection criteria, 1040 individuals were included in the primary analysis, with 49.1% suffered from uncontrolled hypertension (Fig. 1). For the secondary analysis, an additional 241 participants were excluded, resulting in a final sample size of 799 participants, with a total incidence ASCVD rate of 16.0 per 1000-person-year (148/9246.9, 95% CI 13.6–18.8)) and a total death rate of 17.5 per 1000-person-year (172/9846.3, 95% CI 18.8, 27.4) during a median follow-up period of 14.3 years (IQR 10.7–14.6). The follow-up distribution of participants was as follows: 5% (42) were followed over all three follow-ups, 51% (405) were followed over the first two follow-ups, 30% (237) were followed over the first follow-up, and 14% (115) were only followed after the baseline assessment.

Factors associated with uncontrolled hypertension

Participants' characteristics at baseline according to controlled and uncontrolled hypertension are presented in Table 1. Participants with uncontrolled hypertension were older, more frequently men, have a higher BMI, less frequently hold a university degree, less frequently be current smokers, and more frequently report high alcohol consumption.

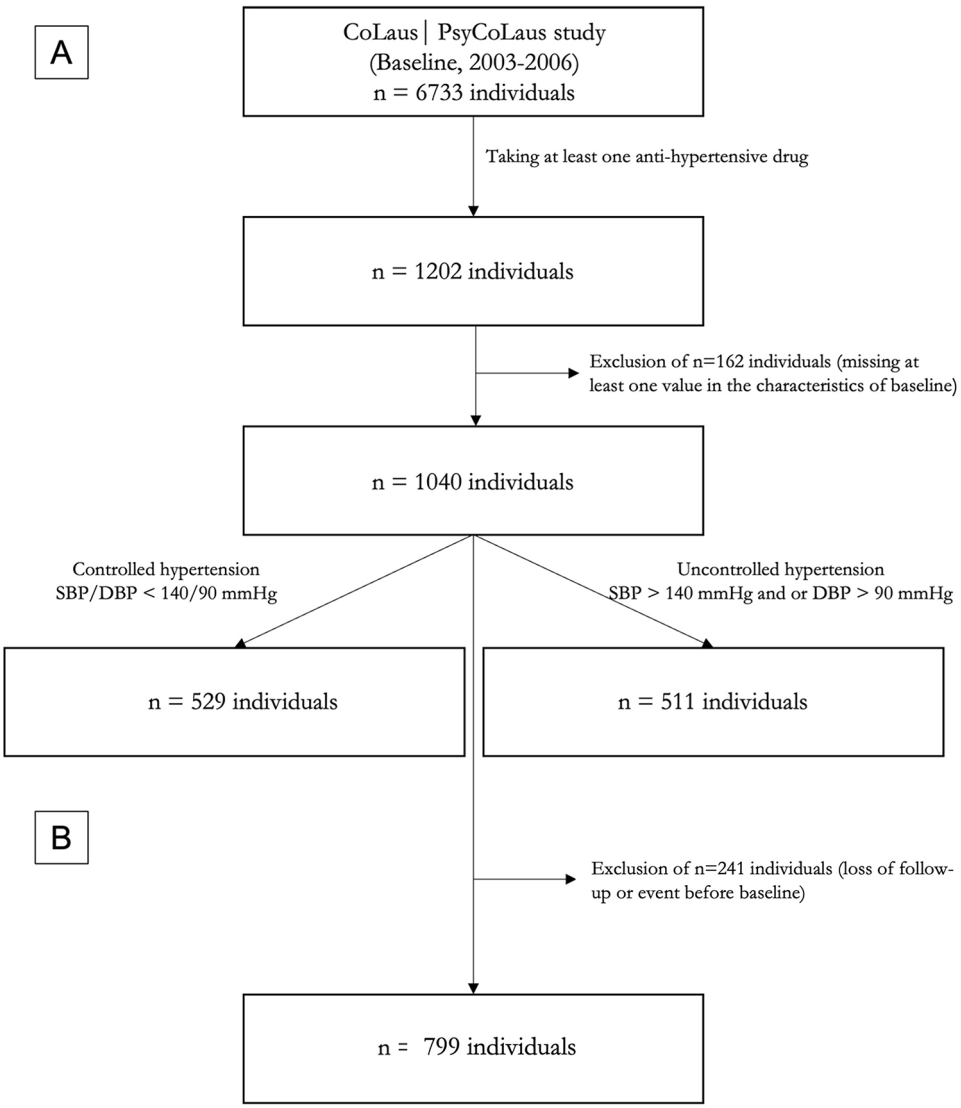


Fig. 1. Flowchart of the sample selection for (**A**) first analysis (association study at baseline), and (**B**) second analysis (association with ASCVD). Legend: The first analysis examined the relationship between uncontrolled hypertension and various socio-economic factors, medical conditions, and biomarkers. The second analysis explored the association between uncontrolled hypertension and the risk of atherosclerotic cardiovascular disease (ASCVD).

	Controlled hypertension	Uncontrolled hypertension	*p*-value
Number of subjects	529 (50.87%)	511 (49.13%)	
Socio-demographic and behavioural factors			
Age (years)—mean	59.8 ± 9.3	61.6 ± 9.1	0.002*
SBP (mm Hg)—mean	125.2 ± 9.7	152.8 ± 14.8	<0.001*
DBP (mm Hg)—mean	76.1 ± 7.7	89.4 ± 10	<0.001*
Sex—n (%)			0.014*
Male	257 (48.6%)	287 (56.2%)	
Female	272 (51.4%)	224 (43.8%)	
BMI—mean	28.1 ± 4.8	28.8 ± 4.8	0.009*
Origin—n (%)			
Caucasian	528 (99.8%)	511 (100%)	
Non-Caucasian	1 (0.2%)	0 (0%)	
Highest education level achieved—n (%)			0.002*
Compulsory education	119 (22.5%)	144 (28.2%)	
Apprenticeship	238 (45%)	221 (43.3%)	
Secondary school	39 (7.4%)	50 (9.8%)	
High school degree	61 (11.5%)	61 (11.9%)	
University degree	72 (13.6%)	35 (6.8%)	
Employment status—n (%)			0.178
Employed	256 (48.4%)	226 (44.2%)	
Unemployed	273 (51.6%)	285 (55.8%)	
Smoking status—n (%)			0.005*
Never	194 (36.7%)	219 (42.9%)	
Former	204 (38.6%)	206 (40.3%)	
Current	131 (24.7%)	86 (16.8%)	
Alcohol consumption (units/week)—n (%)			< 0.001*
None	162 (30.6%)	136 (26.6%)	
1–13	280 (52.9%)	234 (45.8%)	
14–27	63 (11.9%)	101 (19.8%)	
≥ 28	24 (4.6%)	40 (7.8%)	
Caffeine intake (number of cup(s)/day)—n (%)			0.113
None	40 (7.6%)	36 (7.1%)	
1 to 3	342 (64.7%)	364 (71.2%)	
4 to 6	132 (24.9%)	97 (19%)	
≥ 6	15 (2.8%)	14 (2.7%)	
Physical activity (min 20 min/week)—n (%)			0.639
Never	207 (39.1%)	213 (41.7%)	
Once a week	33 (6.3%)	34 (6.7%)	
Twice a week	280 (52.9%)	252 (49.3%)	
Does not know	9 (1.7%)	12 (2.3%)	
Glucose venous (mmol/L) mean	5.9 ± 1.3	6.1 ± 1.6	0.011*
Ferritin (µg/L) median (IQR)	139 (77, 230)	186 (96,328)	< 0.001*
Creatinin (mg/L) mean	82.7 ± 20.7	82.8 ± 23.4	0.959
Urinary Na (mmol/L) mean	105.8 ± 48.6	113.4 ± 47.4	0.011*
Urinary K(mmol/L) mean	74.9 ± 35.4	68.7 ± 34.6	0.005*
Albuminuria (mg/24 h) median (IQR)	8 (4, 14)	9 (5,21)	< 0.001*

Table 1. Participants' characteristics at baseline (2003–2006) according to hypertension control status. Controlled hypertension: BP < 140/90 mm Hg and uncontrolled hypertension SBP ≥ 140 mm Hg, and/or DBP ≥ 90 mm Hg, according to the 2018 and 2021 ESC guidelines for the management of hypertension (https://doi.org/10.1093/eurheartj/ehab484). Results are expressed as number of participants (%) and mean (± SD) except for Ferritin and Albuminuria as they are not normally distributed are expressed in median (IQR). *p*-values were computed using Pearson Chi2 or student t-test when appropriate. BMI, body mass index; Na, sodium; K, potassium. *p value < 0.05 is considered statistically significant.

Table 2 provided results from the different regression models used to assess each variable. After adjusting for sex and age, uncontrolled hypertension was positively associated with alcohol consumption > 14 units/week, increased BMI, increased glycemia, increased urinary sodium excretion, increased ferritinemia and microalbuminuria. Characteristics associated with controlled BP were a high educational level, such as a university degree or an apprenticeship, being a current smoker, and having higher urinary potassium excretion.

After adjusting for sex, age and BMI, urinary sodium excretion and glycemia were no longer statistically associated with uncontrolled hypertension. Previous characteristics associated with controlled BP do not change when adjusted for BMI.

In the third and main model, we included all variables with evidence for an association with uncontrolled BP in model 2. We found that there was still evidence for an association with uncontrolled BP for BMI, alcohol consumption, ferritin, and albuminuria, as well as for university degree, current smoker and urinary potassium.

Stratifying by BMI into three levels (normal, overweight, and obesity) yielded no evidence that the association between smoking status and uncontrolled hypertension differed across BMI categories (likelihood ratio test for

Parameters	Model 1		Model 2		Model 3 (Main model)	
	Odd ratio (95% confidence interval)	*p* value	Odd ratio (95% confidence interval)	*p* value	Odd ratio (95% confidence interval)	*p* value
Sex						
Female					Reference	
Male					1.16 (0.83, 1.63)	0.391
BMI (standard deviation)	1.17 (1.04, 1.31)	0.009*			1.02 (1.01, 1.04)	0.020*
Age (standard deviation)					1.03 (0.99, 1.05)	0.106
Highest education level achieved						
Compulsory education	Reference		Reference		Reference	
Apprenticeship	0.72 (0.53, 0.98)	0.036*	0.73 (0.54, 1.00)	0.053	0.74 (0.54, 1.02)	0.065
Secondary school	1.05 (0.64, 1.71)	0.752	1.12 (0.69, 1.84)	0.644	1.19 (0.72, 1.98)	0.498
High school degree	0.78 (0.50, 1.20)	0.259	0.82 (0.53, 1.28)	0.383	0.89 (0.57, 1.40)	0.611
University degree	0.36 (0.22, 0.59)	< 0.001*	0.39 (0.24, 0.63)	< 0.001*	0.39 (0.24, 0.64)	< 0.001*
Employment status						
Unemployed	Reference		Reference			
Employed	0.98 (0.73, 1.32)	0.904	1.02 (0.76, 1.37)	0.913		
Smoking status						
Never	Reference		Reference		Reference	
Former	0.80 (0.60, 1.06)	0.124	0.80 (0.60, 1.07)	0.133	0.77 (0.58, 1.04)	0.088
Current	0.56 (0.40, 0.79)	0.001*	0.57 (0.41, 0.81)	0.002*	0.53 (0.37, 0.75)	< 0.001*
Alcohol consumption (units/week)						
None	Reference		Reference		Reference	
1–13	0.91 (0.68, 1.22)	0.529	0.92 (0.68, 1.24)	0.589	0.99 (0.73, 1.35)	0.970
14–27	1.69 (1.11, 2.56)	0.013*	1.78 (1.17, 2.70)	0.007*	2.04 (1.31, 3.18)	0.002*
≥ 28	1.74 (0.97, 3.13)	0.064	1.84 (1.02, 3.32)	0.043*	1.84 (0.98, 3.47)	0.059
Caffeine intake (number of cup(s)/day)						
None	Reference		Reference			
1 to 3	1.12 (0.69, 1.81)	0.645	1.08 (0.67, 1.75)	0.745		
4 to 6	0.81 (0.48, 1.37)	0.440	0.80 (0.47, 1.35)	0.396		
≥ 7	1.06 (0.45, 2.51)	0.895	0.99 (0.42, 2.37)	0.987		
Physical activity (min 20 min/week)						
None	Reference		Reference			
Once a week	1.04 (0.62, 1.76)	0.876	1.13 (0.66, 1.91)	0.660		
Twice a week	0.82 (0.63, 1.07)	0.142	0.86 (0.66, 1.12)	0.274		
Glucose venous (standard deviation)	1.11 (1.01, 1.23)	0.038*	1.08 (0.97, 1.19)	0.168		
Ferritin (standard deviation)	1.23 (1.09, 1.38)	0.001*	1.21 (1.08, 1.37)	0.001*	1.15 (1.01, 1.30)	0.029*
Creatinin (standard deviation)	0.90 (0.79, 1.04)	0.156	0.90 (0.78, 1.03)	0.132		
Urinary sodium (standard deviation)	1.16 (1.02, 1.32)	0.021*	1.13 (0.99, 1.28)	0.066		
Urinary potassium (standard deviation)	0.82 (0.72, 0.93)	0.003*	0.83 (0.72, 0.94)	0.004*	0.79 (0.69, 0.91)	0.001*
Albuminuria (standard deviation)	1.22 (1.04, 1.42)	0.014*	1.21 (1.03, 1.41)	0.017*	1.20 (1.02, 1.40)	0.031*

Table 2. Association between sociodemographic, behavioural, and biological characteristics with uncontrolled blood pressure at baseline (2003–2009) adjusted for sex and age (Model 1), sex, age and BMI (Model 2) and all significant characteristics (Model 3). *p value < 0.05 is considered statistically significant.

interaction, p-value = 0.1). The adjusted odds ratios for the association between current smokers compared to non/former smokers and uncontrolled hypertension among individuals with normal weight, overweight, and obesity were 0.63 (95% CI 0.45–0.88), 0.65 (95% CI 0.40–1.08), and 0.94 (95% CI 0.53–1.69), respectively.

Prospective associations between uncontrolled hypertension and development of ASCVD, and all-cause mortality

There was a lack of evidence to support a difference in the rate of incident events or all-cause mortality between individuals with uncontrolled hypertension and those with controlled hypertension with hazard ratios [HR] of 1.02 (95% CI, 0.73–1.44) and 1.14 (95% CI, 0.83–1.58) respectively (Fig. 2).

In the sensitivity analysis with time-varying exposure, the missing data for updated hypertension status were 29%, 7%, and 90% for participants followed during the respective follow-up periods: one (2009–2012), two (2014–2017), and three (2018–2021). Regarding changes in hypertension status, 60% of participants had no change in hypertension status, irrespective of the number of updates, while 32% experienced one change, and 9% experienced two changes. After the first follow-up, 13% of participants changed from uncontrolled to controlled hypertension status, and 16% experienced the opposite change. These figures were 8% and 10% after the second follow-up. After the third follow-up, only 0.2% changed from uncontrolled to controlled hypertension, and 0% changed from controlled to uncontrolled hypertension. There was also insufficient evidence to support an association between uncontrolled hypertension status and an increased risk of incident ASCVD (HR 1.10, 95% CI 0.78–1.58, p-value 0.6).

Lastly, there was no difference in the estimates when the number and type of antihypertensive medications were included in the fixed and time-varying regression models.

Discussion

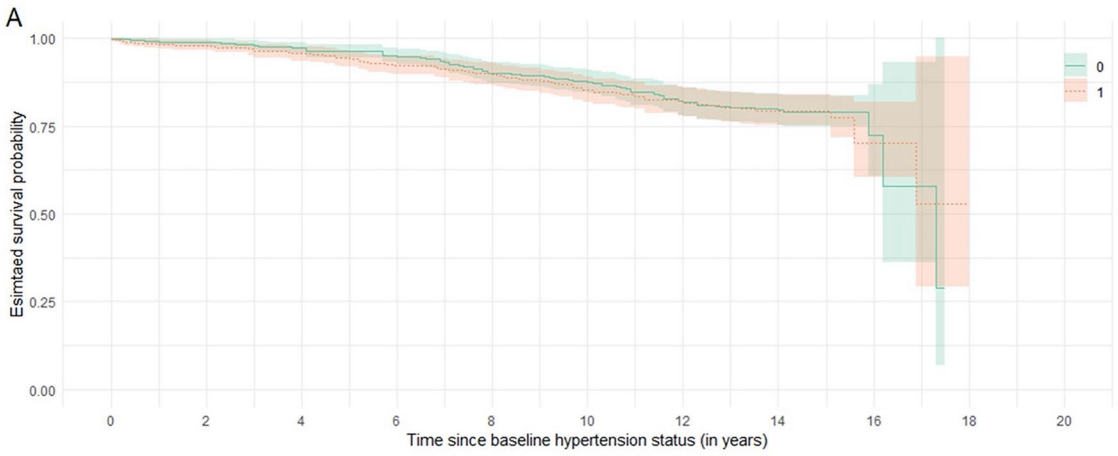
Our findings, based on contemporaneous data from the community, showed that modifiable behavioural and biological factors, such as heavy alcohol consumption, overweight, ferritinemia and albuminuria, were associated with an increased risk of uncontrolled hypertension. Factors associated with adequate BP control were education, such as a university degree, being a current smoker and high potassium urinary excretion. Our study sample provides insufficient evidence that baseline uncontrolled hypertension was associated with incident ASCVD or all-cause mortality.

In terms of modifiable factors associated with uncontrolled hypertension status, our findings show an association with heavy alcohol consumption. Individuals consuming more than 14 units per week exhibited a 2.04-fold increase in the relative odds of poor blood pressure control compared to teetotalers, consistent with prior research[14]. Roerecke et al. conducted a meta-analysis demonstrating an average decrease in SBP of 5.5 mm Hg and DBP of 4.0 mm Hg among individuals who reduced their alcohol intake from over six drinks per day[15]. Additionally, for each increase in 1 standard deviation (SD) of BMI (equivalent to 4.5 kg/m^2), the likelihood of poor blood pressure control increased by 1 to 4%, aligning with previous reports[7,16]. Our study also replicated previous results presenting a counterintuitive association between current smokers with a lower risk of having uncontrolled hypertension compared to non/former smokers, even after adjusting for several variables[17–19]. This observed effect of smoking could, in part, be attributed to BMI, with a protective effect persisting only in people of normal weight. However, our study may not have sufficient statistical power to conclusively demonstrate this variation, already observed in another study[20]. However, other studies found an association between lifetime cigarette consumption with hypertension[16,20,21]. This discrepancy could stem from the effect of smoking on blood pressure regulation through different physiological mechanisms over time. In cross-sectional studies like ours, the observed effect may be due to the current depressant effect induced by nicotine, resulting in a temporary reduction in blood pressure. However, the direct impact of carbon monoxide on the arterial wall could lead to structurally irreversible alterations over time, potentially increasing the risk of significant hypertension in the long term. These findings align with those found when assessing the long-term effects of smoking intensity over time[16,22]. Consequently, being a current smoker could falsely reassure regarding hypertension management during a general practitioner consultation and obscure the true extent of damage over time[21].

Among the remaining socio-demographic and behavioral factors, having a university degree was associated with a 0.39-fold reduced risk of uncontrolled hypertension compared to individuals with only compulsory education. Zheng et al. observed an increased in BP control among Chinese individuals with higher education relative to those with only primary education[23]. Sun et al. showed that the individuals with only compulsory education had not only an increased risk of being diagnosed with hypertension but had higher difficulty to control BP[24]. Moreover, hypertension partially explains the causal association between education level and atherosclerotic cardiovascular disease through unhealthy behaviors such as an imbalanced diet and low physical activity[25].

No association between physical activity and uncontrolled hypertension was found in our study. However, previous studies have reported relationships between different intensities of physical activity and blood pressure control, including reduced reliance on antihypertensive medication among those engaging in regular moderate-intensity exercise[6,26,27]. Our results might be explained by the fact that physical activity was self-reported by participants and that we do not have information on the intensity of the latter.

Investigating potential biomarker to target at risk-individuals for uncontrolled hypertension, we found that a 1-SD increase in ferritin level was associated with a 1.15-fold risk of having uncontrolled hypertension, consistent with existing the literature[28]. Although iron metabolism is implicated in many pathophysiological processes, including inflammation[28–30], its association with hypertension status remains debated. Studies suggested that a higher level of ferritin might promote oxidative stress leading to endothelial damage and thus contributing to rising BP[31]. We confirmed an association between urinary potassium excretion and hypertension status, a 1-SD increase in urinary potassium excretion (= 36.6 mmol/L) being associated with a 20% decrease of having

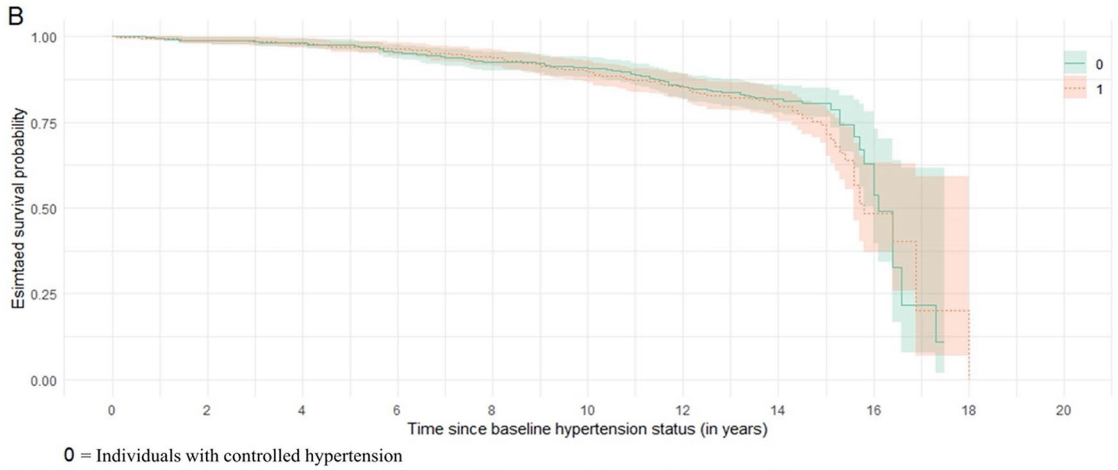


0 = Individuals with controlled hypertension

At risk	403	395	387	341	321	308	227	208	8	0	0
Censored	0	4	6	43	46	50	113	126	324	330	330
Events	1	5	11	20	37	46	64	70	72	74	74

1 = Individuals with uncontrolled hypertension

At risk	394	383	372	335	317	295	198	175	11	0	0
Censored	0	4	6	30	39	46	132	150	311	321	321
Events	1	8	17	30	39	54	65	70	73	74	74



0 = Individuals with controlled hypertension

At risk	404	399	396	353	343	336	257	240	11	0	0
Censored	0	1	1	33	33	33	94	101	319	325	325
Events	0	4	7	18	28	35	53	63	74	79	79

1 = Individuals with uncontrolled hypertension

At risk	395	391	386	359	348	333	229	203	12	0	0
Censored	0	0	1	22	23	23	113	124	294	302	302
Events	0	4	8	14	24	39	53	68	89	93	93

Fig. 2. Predicted survival curves from Kaplan Meier for (**A**) incident ASCVD (**B**) all-cause mortality in individuals with 1. Uncontrolled hypertension vs. 0.controlled hypertension. Legend: The curves illustrate the survival probabilities over time of follow-up for each group between those with uncontrolled and controlled hypertension.

uncontrolled hypertension[8]. This finding aligns with a meta-analysis that advocated for increased potassium intake as a consideration for hypertension prevention and treatment[32]. Given its significance, urinary potassium excretion could serve as a valuable marker for evaluating risk of uncontrolled hypertension.

We observed a positive association between glycemia and uncontrolled hypertension when adjusted for sex and age, which disappeared when adjusting for BMI. This finding may be explained by the prevalence of prediabetes and type 2 diabetes in overweight and obese populations[33]. Additionally, we found no evidence of an association between urinary sodium (a marker of dietary habits) and uncontrolled blood pressure after adjusting for BMI, contrary to previous studies[8]. This result aligns with the known positive association between sodium consumption and BMI[8,34].

Our study sample provides insufficient evidence to support an association between controlled hypertension and a lower risk of incident ASCVD or all-cause mortality, contrary to finding from previous literature[35]. Zhou et al., reported that among 13,947 adults in the United States, individuals with uncontrolled hypertension had a higher risk of all-cause mortality compared untreated normotensive individuals. However, their study did not directly compare controlled and uncontrolled hypertensive individuals[36]. Additionally, previous studies were based on cohorts recruited 30–40 years ago[36–39]. Advances in cardiovascular disease prevention and treatment may have reduced the impact of uncontrolled hypertension or improved cardiovascular care for those with evident uncontrolled hypertension. Consequently, the effect size of controlled hypertension might be smaller than observed in earlier studies, and a larger sample size may be required to provide sufficient power to confirm an association, even when adjusting for time-varying exposure. Furthermore, general practitioners (GP) were informed about the result of BP measurement. Therefore, they could freely decide to increase anti-hypertensive drug or implement other interventions (dietary habit, physical activity, weight loss). The awareness of uncontrolled hypertension could prompt GPs and patients to engage in lifestyle changes or more regular personalized prevention measures, potentially reducing the risk of CVD to a level comparable to those with controlled hypertension in our sample.

Conclusion

In a contemporaneous population-based cohort, uncontrolled blood pressure was still associated with modifiable factors at both individual and population levels, such as heavy drinking, obesity, level of education, and uncontrolled hypertension. There was a lack of association between controlled hypertension and the risk of incident ASCVD or all-cause mortality.

Strength and limitations

The strength of our study is its confirmation, using a contemporaneous sample, of the socio-demographic and biological factors associated with uncontrolled hypertension. The main limitation is the cross-sectional design, which restricts our ability to rule out reverse causation and residual confounding. We recognize that using 24-h ambulatory blood pressure monitoring (ABPM) would have provided a more accurate assessment of hypertension status and limited misclassification. Additionally, data on therapeutic adherence were unavailable, which could have impacted the association between uncontrolled hypertension and ASCVD/mortality rates. Furthermore, 12% of our prospective sample was excluded due to loss to follow-up, potentially biasing the results. Finally, most participants were Caucasian, limiting the applicability of the findings to other ethnicities and contexts.

Methods

Study participants

The CoLaus|PsyCoLaus study is a Swiss prospective population-based cohort designed to investigate ASCVD and their risk factors, such as hypertension[40]. 6733 subjects, aged 35–75 years at baseline (2003–2006), were randomly selected from the population of Lausanne (Switzerland). Participants performed a clinical assessment, completed questionnaires, and had a blood sample collection. Three follow-ups (2009–2012, 2014–2016 and 2019–2021) with clinical examination, blood sample and questionnaire collection, were conducted. ASCVD events and deaths were prospectively collected and adjudicated as described previously[41]. The cantonal Ethics Commission approved the CoLaus|PsyCoLaus study (http://www.cer-vd.ch) project number PB_2018-00038, reference 239/09), and all participants provided written informed consent.

Inclusion and exclusion criteria

We included individuals from baseline (2003–2006) treated with at least one anti-hypertensive drug, comprising angiotensin-converting enzyme (ACE) inhibitors, angiotensin II receptor blockers, aldosterone antagonists, thiazide derivatives and other diuretics, calcium channel blockers and alpha/beta-blocking agents, according to ATC coding (https://www.whocc.no/atc_ddd_index/).

For the main aim (i.e., investigating the association between uncontrolled hypertension status and a range of socio-economic, medical conditions and biomarkers), we excluded all individuals with at least one missing value on the selected characteristics at baseline comprising age, sex, ethnicity, smoking status, alcohol consumption, caffeine intake, employment status, education level, physical activity, glycemia, ferritin, creatinine, urinary sodium and potassium, albuminuria and body mass index (BMI).

For the second aim (i.e., investigating whether uncontrolled hypertension is associated with ASCVD), in addition, we excluded subjects with prevalent ASCVD at baseline and/or without follow-up ascertainment.

Characteristics and outcome measurements

Participants were invited to the outpatient clinic at Lausanne University Hospital in the morning following an overnight fast for comprehensive clinical assessment, questionnaire completion, and blood sample collection. Demographic, socio-economic factors were recorded, including age, sex, ethnicity (Caucasian or non-Caucasian), current smoking status (never, former, current), alcohol consumption (none, 1–13 units/week, 14–27 units/

week, > 28 units/week), caffein intake (none, 1 to 3, 4 to 6 and > 6), employment status (unemployed versus employed), education level (ranging from compulsory education to university degree), and physical activity level (ranging from none to twice a week, with an additional option for uncertain activity levels). Additionally, participants provided information on their use of antihypertensive medications.

Blood pressure was measured by a trained research nurse. Blood pressure and heart rate were measured thrice on the left arm with appropriately sized cuff after at least 10 min rest in seated position, using a Ormon HEM-907 automated oscillometric sphygmomanometer. The average of the last two measurements was used for analyses. Uncontrolled hypertension was defined as a systolic BP (SBP) ≥ 140 mm Hg and/or a diastolic BP (DBP) ≥ 90 mm Hg during the visit.

In addition, BMI was calculated using measurements of height and weight. Furthermore, venous blood samples (50 mL) were drawn after an overnight fast, and most clinical chemistry assays were performed by the CHUV Clinical Laboratory on fresh blood samples and spot urine samples to collect glycemia, ferritin, creatinine, urinary sodium and potassium and albuminuria[40].

Statistical analysis

Stata 17.0 (Stata Corporation, College Station, Texas, USA) was used for analyses. Baseline participants' characteristics were expressed as a number (percentage) for categorical variables, mean ± standard deviation (SD) for continuous normally distributed variables or median, interquartile range (IQR) for not normally distributed variables and were stratified by hypertension status (uncontrolled vs. controlled hypertension). Pearson chi-square, Student t-test or Rank Sum test were used to evaluate differences in subjects' baseline characteristics according to hypertension status.

As age and sex are well-known to influence socio-economic and medical conditions, these 2 variables were included as potential confounders in the first regression model (Model 1) assessing the association of each factor with hypertension status. BMI is a commonly known risk factor associated with hypertension[42], as well as other metabolic diseases such as type 2 diabetes[43] and chronic renal disease[44] and with behavioral factors such as physical activities or dietary habits[45]. Therefore, we added it as potential confounder in a second model (Model 2) which assessed the association for each factor.

In addition, previous studies have found associations between alcohol intake, employment status, education level, and hypertension[14,23,24,46]. Interestingly, studies have also reported a counterintuitive finding: current smokers appear to have a lower risk of uncontrolled hypertension compared to non-smokers and former smokers, even after adjusting for multiple variables.

Finally, a third model (Model 3, the main model) was performed by including all factors that were individually associated with hypertension status in Model 2. Odds ratios from logistic regression for categorical factors and linear regression for continuous factor were presented along with a 95% confidence interval, and for all analyses, $p \leq 0.05$ was considered as some evidence for an association.

To facilitate regression's coefficients interpretation and comparison, continuous variables were standardized (variables were divided by their SD, i.e., age SD = 10.7 years, BMI SD = 4.5 kg/m^2, glucose SD = 1.2 mmol/L, ferritinemia SD = 180.5 ug/L, creatinine SD = 21.2 mg/L, urinary sodium SD = 48.6 mmol/L, urinary potassium SD = 36.6 mmol/L and microalbuminuria SD = 76.4 mg/day). Standard deviations were derived from the whole sample of CoLaus|PsyCoLaus (n = 6733).

Given the association we observed, where current smokers had a lower likelihood of having uncontrolled hypertension, we pursued additional exploratory investigations. Considering the pronounced effect of smoking on weight and the strong association between weight and SBP regulation, we sought to examine how smoking interacts with weight. Thus, we reclassified the smoking status into "current smokers" and "non-smokers or former smokers," while BMI was stratified into three categories: normal (BMI < 25 kg/m^2), overweight (25–30 kg/m^2), and obesity (BMI > 30 kg/m^2). We assessed evidence for interaction through likelihood ratio tests.

For the second aim, Cox proportional hazards regressions was performed to evaluate the association between hypertension status and incident ASCVD, as well as all-cause mortality. Predicted survivor curves were computed with Kaplan–Meier methods. Comparison of survival functions was assessed with a log-rank test and Cox proportional hazards models adjusted with the co-variables which were evidence for an association with hypertension status in Model 3: BMI, alcohol consumption, education level, smoking status, potassium urinary excretion, ferritin and albuminuria. The proportionality assumption was inspected using the scaled Schoenfeld residuals. As blood pressure control may change over the follow-up period, we conducted a sensitivity analysis on incident ASCVD, allowing the exposure status for each individual to vary over time. Hypertension status was extracted for each follow-up (i.e., 2009–2012; 2014–2017; 2018–2021), resulting in a maximum of four interval periods of potentially different hypertension statuses before an incident ASCVD event or censoring. We used a random effects Poisson regression model, assuming the random effects follow a Gamma distribution to account for within-participant clustering of hypertension status. This analysis was adjusted for the same covariates as in the Cox regression model, in addition to the participant's current age in five-year age ranges, to account for the age-range varying effect of exposure on incident ASCVD. Lastly, we performed a sensitivity analysis using Cox regression with both single-point and time-varying exposure measurements, adjusting for the number (1 vs. 2 or more) and type of antihypertensive medications (beta-blockers and angiotensin-aldosterone system blockers, known to improve cardiovascular survival, vs. others like diuretics or calcium channel blockers).

All research was performed in accordance with relevant guidelines/regulations.

Data availability

The data that support the findings of this study are available from the CoLaus study but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the corresponding author upon reasonable request and with permission of the

Colaus study. Instructions for gaining access to the CoLaus data used in this study are available at https://www.colaus-psycolaus.ch/professionals/how-to-collaborate/.

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Disclaimer
The data of CoLaus|PsyCoLaus study used in this article cannot be fully shared as they contain potentially sensitive personal information on participants. According to the Ethics Committee for Research of the Canton of Vaud, sharing these data would be a violation of the Swiss legislation with respect to privacy protection. However, coded individual-level data that do not allow researchers to identify participants are available upon request to researchers who meet the criteria for data sharing of the CoLaus|PsyCoLaus Datacenter (CHUV, Lausanne, Switzerland). Any researcher affiliated to a public or private research institution who complies with the CoLaus|PsyCoLaus standards can submit a research application to research.colaus@chuv.ch or research.psycolaus@chuv.ch. Proposals requiring baseline data only will be evaluated by the baseline (local) Scientific Committee (SC) of the CoLaus and PsyCoLaus studies. Proposals requiring follow-up data will be evaluated by the follow-up (multicentric) SC of the CoLaus|PsyCoLaus cohort study. Detailed instructions for gaining access to the CoLaus|PsyCoLaus data used in this study are available at www.colaus-psycolaus.ch/professionals/how-to-collaborate/.

Author contributions
S. RdM collected underlying data, performed statistical analysis and visualization, interpreted the results and wrote the original draf preparation. R. DLH performed statistical analysis and visualization. All authors contributed to design of the study and revised the manuscript for important intellectual content. J.V. conceived the original idea of the study, collected data and supervised. J.V. and P.V. had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests
The authors declare no competing interests.

Additional information
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